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08/087,132 07/02/93 GREGORY

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EXAMINER
CARLSON, K

18N2/1209

ART UNIT PAPER NUMBER

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1812

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DATE MAILED:

12/09/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on #19, 22, 23 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input checked="" type="checkbox"/> <u>Examiners Interview Summary</u> |

Papers # 20, 21, & 24

Part II SUMMARY OF ACTION

1. ☒ Claims 139-163 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-138 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 139-163 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

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This Office Action is in response to Paper #19 (filed October 3, 1994), Paper #22 (filed October 27, 1994), and Paper #23 (filed November 17, 1994). Claims 1-138 have been cancelled. Claims 139-163 are currently pending and under examination.

5 The priority date of the instant invention is March 5, 1990, the filing date of parent application S.N. 488,307

*All previous rejections and objections concerning the patentability of the Claims are withdrawn and **finality** is removed.*

10

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

15

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed. The specification teaches how to introduce a specific intron or double point mutations into DNA encoding CFTR to stabilize the DNA or aid in its propagation without the expression of functional CFTR protein which is toxic in E. coli and reduces its growth. The specification also teaches the use of low copy vectors for the same goal. The specification does not teach how to introduce a specific intron or double point mutations into DNA encoding CFTR or the use of low copy vectors to aid in the maintenance or insertion or stable transformation of the DNA encoding CFTR into the bacterial genome. Therefore, Claims directed to the modifications in the DNA sequence such that the DNA maintenance is facilitated in bacteria

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considered to be new matter.

Claims 139-150, 152-156, and 161 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

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Note: to advance the prosecution of the application, the Examiner has taken "maintenance" to be "propagated" for Claims 139-156 and 160-163 for the rejection of these Claims under 35 USC 112, first paragraph, relating to the scope or breadth of the Claims.

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Claims 139-163 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to DNA encoding huCFTR having the sequence set forth in Table 1, the intron set forth in Fig. 6, point mutations T748C with A774G, and E.coli. See M.P.E.P. §§ 706.03(n) and 706.03(z).

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Claims 139, 144, 151, 155, and 157-160 recite that the DNA encodes an "amino acid sequence sufficiently duplicative of human CFTR". The specification only teaches using DNA encoding huCFTR as set forth in Table 1. No guidance is provided in the specification as to what DNA sequence encodes a huCFTR that is sufficiently like huCFTR. That is, the specification teaches no other analogous huCFTR and does not teach how to modify the DNA encoding huCFTR so that this new huCFTR acts like the huCFTR set forth in Table 1. It is not predictable if a N-terminally truncated huCFTR or a mid-sequence deletion of 20 amino acids acts like the full-length huCFTR of Table 1, for example. Indeed, even the deletion of a single amino acid such as Phe508 will inactivate the CFTR as this mutation is responsible for the symptoms of CF and, being only a single amino acid deletion, would be "sufficiently

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5 duplicative" of huCFTR to meet this particular limitation. See Riordan et al. (1989) below. Without sufficient guidance, it would require undue experimentation for one of ordinary skill in the art to determine what modifications can be done to the huCFTR of Table 1 such that the modified huCFTR acts like the huCFTR of Table 1.

Claims 130 and 144 state that the DNA encoding CFTR will be modified, The only modification of this DNA is the insertion of an intron of Fig. 6 and two point mutations. To this end, the contents of the next two paragraphs are incorporated in the discussion of the breadth of these Claims.

10 Claims 140, 141, and 163 state that the modification will be an intron or synthetic intron. Only the intron of Fig. 6 has been shown to enhance the growth of E. coli transfected with DNA encoding huCFTR and this intron by preventing the expression of the CFTR protein. It is not predictable if a small intervening sequence or intron will sufficiently disrupt the protein
15 synthesis and subsequent host cell death as only the 83 bp synthetic intron of Fig. 6 has been shown prevent E.coli cell death. There is no guidance as to whether endogenous introns to the huCFTR gene are adequate to prevent CFTR expression or if there will be "read through" and additional amino acids placed between amino acids of huCFTR such that CFTR activity is not affected,
20 for example. There is no guidance as to what comprises a "synthetic" intron such that CFTR protein synthesis is prevented as is its toxicity. Are the codons random or in a specific sequence and does it matter? It would require undue experimentation for one of ordinary skill in the art to determine what comprises in intron such that functional CFTR is not expressed in bacterial
25 cells because no guidance is provided in the specification and determination of what comprises such an intron is not predictable.

Claims 142, 143, 145 and 162 are directed to point or silent mutations placed in the DNA encoding huCFTR such that the functional CFTR is not

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expressed in bacterial cells. The DNA encoding CFTR is over 6000 bp in length. Only a double point mutation has been shown to prevent CFTR expression, these mutations being in the cryptic bacterial promoter at positions 748 and 774. This is not sufficient evidence such that one of
5 ordinary skill in the art could reasonably place a point or silent mutation anywhere among the 6000 bases and expect that the DNA will be propagated within the bacterial host cell without expressing the E. coli toxic CFTR. Silent mutations that do not effect the transcriptional regulation of the DNA encoding CFTR would be expected not to prevent the expression of the toxic
10 CFTR. Point mutations where only one of over 1400 amino acids would not be expected to alter the activity of the expressed CFTR. Without guidance in the specification, it is not predictable what base mutation will prevent CFTR expression in bacteria and undue experimentation would be incurred for one of ordinary skill in the art to make all possible mutations and determine if the
15 CFTR will be produced in functional form and be toxic to the bacterial cell.

In all Claims, the host cell will be limited to E. coli. In Example 6, page 16, line 14+, the specification teaches that "although CFTR cDNA displays apparent toxicity in E. coli cells, other types of host cells may not be affected this way. Alternative host systems in which the entire CFTR cDNA
20 protein encoding region may be maintained and/or expressed include other bacterial species and yeast. It is not possible to a priori predict which cells might be resistant and which might not". Given the unpredictability of the susceptibility of host cells to CFTR, it would require undue experimentation to determine if the DNA encoding CFTR could be transfected
25 into Pseudomonas, for example, and the Pseudomonas continue to grow if CFTR is expressed. Additionally, because the mutations were placed within the cryptic promoter of E. coli and this promoter is only responsive in E. coli, then the point mutations disclosed would be ineffective in preventing CFTR expression

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in *Pseudomonas*. This same analogy may be made with the intron.

Claims 147, 154, 155, and 159 are rejected under 35 U.S.C. § 112, second
5 paragraph, as being indefinite for failing to particularly point out and
distinctly claim the subject matter which applicant regards as the invention.
Claim 147 is directed to DNA further comprising a recoverable clone. This is
indefinite because clones comprise DNA, not vice versa. Claims 154, 155, and
159 are indefinite because these Claims are directed to a composition which
10 must comprise at least two entities rather than the single entity recited in
the Claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C.
§ 102 that form the basis for the rejections under this section made in this
15 Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or
20 patented or described in a printed publication in this or a foreign
country, before the invention thereof by the applicant for a patent.

Claims 139, 140, 146, and 150 are rejected under 35 U.S.C. § 102(a) as
being anticipated by Riordan et al. (1989). Riordan et al. teach that CFTR is
a 1480 amino acid protein encoded by a 6.1 kb DNA molecule. Riordan et al.
teach that genomic DNA encoding CFTR has 24 exons and therefore 22 introns
25 (page 1067, col. 1; Fig. 1; Claims 139, 140). Riordan et al. teach the RNA
encoding CFTR is isolated in a single band (page 1067, col. 1-2; Claim 150).

Applicants argue in Paper #19 that Riordan et al. do not teach that the
introns will allow the propagation of the DNA encoding CFTR in bacterial
30 cells. Riordan et al. did not transfect bacterial cell with DNA encoding CFTR
having an inserted intron. These are product claims and the burden is shifted

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to Applicants to point out why endogenous introns would not be expected to prevent functional CFTR expression in bacteria.

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10 Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D., whose telephone number is (703) 308-0034. The Examiner can normally be reached Monday through Thursday from 7:00 A.M. to 4:30 P.M. The Examiner can also be reached on alternate Fridays.

15 If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette D. Draper, can be reached at (703) 308-4232. The fax phone number for Group 180 is (703)305-3014.

20 Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

*rec
12-1-94*

Stephen Walsh

**STEPHEN G. WALSH
PRIMARY EXAMINER
GROUP 1800**